Non-Compliance with childhood acute lymphoblastic leukemia treatment in Indonesia

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2009

CHAPTER 7

A medication diary-book for parents of childhood acute lymphoblastic leukemia patients in Indonesia: treatment outcome from a randomized trial

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Submitted

ABSTRACT

Background

Event-free survival of childhood acute lymphoblastic leukemia (ALL) in Yogyakarta, Indonesia was low (20%). The aim of the study was to evaluate the effectiveness of using a diary-book in the outcome of childhood ALL.

Methods

A randomized study was conducted with 109 childhood ALL patients in a pediatric oncology centre in Yogyakarta, Indonesia. Both the intervention and the control groups received a structured parental education program and donated chemotherapy. The intervention group received a medication-diary book to assist reminding parents and families to take oral chemotherapy and present for scheduled appointments or admissions. Event-free survival estimate (EFS) at 3 years was assessed.

Results

Among childhood ALL patients whose mothers had a high educational level (senior high school or higher), the EFS estimate at 3 year in the intervention group was significantly higher that the EFS estimate in the control group (62% vs. 29%, p=0.04). No significant difference was found in EFS estimate at 3 years between the intervention and the control groups in childhood ALL whose mothers had low educational level (26% vs. 18%, p=0.86)

Conclusions

In a resource-limited setting, a medication-diary book is useful to improve the EFS estimate in childhood ALL patients especially in those whose mothers had a high education level. For parents with a lower educational level the diaries should be made simpler, and more support and education is necessary to help them to use it.

Keywords: Medication-diary book, childhood acute lymphoblastic leukemia, treatment outcome

BACKGROUND

Non-compliance with prescribed drugs becomes an increasingly important issue in treating childhood ALL. Since self-administration of oral chemotherapy for a long period is required, it has become consistently apparent that many patients do not take medication completely[1]. Childhood ALL is universally treated according to defined protocols. After achieving complete remission, ALL patients

must take oral medication for at least 2 years of treatment to prevent relapse. Similar to other chronic diseases, such as asthma, tuberculosis, and epilepsy, non-compliance with prolonged treatment is a problem. It is illogical to assume that ALL patient, regardless of the life-threatening disease, will really take the medication daily for 2 years, especially because they are in relatively good health after achieving complete remission and suffer no immediate consequences when doses of drugs are missed[2].

Our previous medical records study found that event-free survival (EFS) was 20%. Treatment refusal or abandonment was the most common cause of treatment failure in Yogyakarta, Indonesia, where 35% of patients refused or abandoned treatment. There were significant differences in EFS rates between poor and prosperous patients and between patients with different level of education. There were also differences in individualized attention from oncologists and structured parental education. Most poor patients could not afford treatment and access to donated chemotherapy was inadequate[3]. We suppose that non-compliance is an important cause of treatment failure. To improve compliance, decrease abandonment rate and subsequently improve the survival rate, a program was instituted in January 2004 at Dr. Sardjito Hospital, Yogyakarta. It consists of a structured parental education-program (PEP) and donation of chemotherapy for all new ALL patients. In addition to this program, a randomized study by providing a medication diary-book for assigned ALL new patients was conducted.

Studies on interventions to improve compliance and treatment outcome found that the interventions were complex and labors-intensive. It included various combinations of: education, counseling, reminders, self-monitoring, reinforcement, family therapy, and additional support or attention[4-6]. Some studies assessing the use of diary-books in health have been conducted; a pain-diary book to decrease pain intensity[7;8], a symptoms monitoring-diary book in adult cancer patients[9], a diary-book to improve medicine compliance in rhinitis patients[10], and a diary-book in asthma patients[11]. However, none assessed the use of a diary book in treatment outcome of childhood ALL patients. In this study, a diary-book was provided to randomly assigned childhood ALL patients as a reminder to take oral chemotherapy and visit the hospital on schedule. The control group received PEP and donation chemotherapy only, the intervention group receive additionally a diary-book. We tested the hypothesis that patients who received a medication diary-book would have better EFS that patients who did not receive it.

METHODS

Setting

The study was conducted at the pediatric department of Dr. Sardjito Hospital in Yogyakarta, Indonesia. The Hospital is both a teaching hospital of the Medical Faculty of the Gadjah Mada University, and a tertiary-care referral hospital of the Yogyakarta and Central Java Provinces. Annually, approximately 30-50 children are diagnosed with ALL. The pediatric department consists of a clinic (VIP, 1st, 2nd, and 3rd class) and a policlinic (VIP and general). VIP and 1st class patients can chose their own pediatric oncologist. The 2nd and 3rd class patients attend the clinic and general policlinic where they are treated by monthly rotating pediatric residents. One consistent nurse worked at the general policlinic. Most patients were hospitalized at the 3rd class and visited the general policlinic.

During our research period 2 successive ALL protocols were used: the Wijaya-Kusuma ALL protocol (January 2004 to December 2005) and starting from January 2006 the Indonesia-ALL-2006 protocol. The latter protocol is more intensive, in which daunorubicin and L-Asparaginase are added in the induction phase and high-dose methotrexate is added in the consolidation phase. Both protocols used the same risk stratification, based upon NCI criteria plus day 8 blast count and patients were thus stratified into standard risk (SR) and high risk (HR). Both protocols consist of an induction, consolidation, and maintenance phase, with an additional re-induction phase for HR patients.

Design

The study was a randomized clinical trial evaluating the effectiveness of a medication diary-book on the outcome of childhood acute lymphoblastic leukemia in Indonesia. Patients who were diagnosed with ALL between January 2004 and February 2007 and aged 0-16 years old were enrolled on the study. Based on our previous study we learned that some patients abandoned or died in the first week of treatment. To prevent the confounding factors of treatment failure, only patients who achieved the second-week of treatment were randomized either into the diary-book group or into the control group. Randomization was stratified based on risk stratification to prevent possible interaction between the risk stratification and assignment diary group.

Procedure

After the diagnosis was established, parents of childhood ALL received a structured PEP. The program consisted of a multi-method approach: verbal explanation, information-booklet, information-audiocassette and information-DVD. It explained the disease, its treatment, possible side-effects, importance to comply, and experience of parents who completed the treatment. It also gave information about the right to get free chemotherapy for all ALL patients. In addition to this PEP, parents of patients who were assigned to the intervention group received a medication diary-book. A social-pediatrician provided PEP and explained the aims of using the diary-book and demonstrated how to fill the diary. A trained-oncology nurse and technician-laborant who worked at the pediatric hemato-oncology department were instructed to check whether parents filled in the diaries during controls/follow up and to put their signature on the day of control in the diary. Patients were encouraged to bring the diary-book during hospital visits in order to be checked by the oncology-nurse and technician-laborant.. At the end of the PEP session, parents were asked to a sign informed-consent and a statement of understanding with Estella Fund about donated chemotherapy.

Demographic and medical data regarding information on age, gender, parental educational status, socio-economic status, risk-stratification, protocol-use and treatment outcome were obtained from the patients' medical records. Parental educational status was categorized into low education status (no education, elementary school, junior high school) and high education status (senior high school, academy, university). We classified the SES as either poor or prosperous. This classification was based on 2 determinants: monthly income level of parents and assigned hospital class during the diagnostic process. Both determinants are obtained routinely during admission to the clinic and recorded in the medical records. The threshold per month income for poor versus prosperous families was set at 1.000.000 Indonesian Rupiah (about 100 US dollar). Patients attending VIP, and first class wards and VIP policlinic were classified as prosperous. In case with discordance between family income and hospitalization class or data of family income is not available, we used hospitalization class as SES determinant. The study was approved by the Medical Ethics Committee of the Medical Faculty of Gadjah Mada University.

The medication diary-book

We developed a medication diary-book based on the protocol. The medication diary-book is a small (12 x 20) cm and light book, in order make it easier to bring and keep it in a bag. In general, it consists of 2 sections: a form in which parents only fill a mark (v) per day if oral chemotherapy has been taken and a section in which parents can write any information (reasons for not taking the medication, symptoms, laboratory results, procedures and others). The last section was voluntary written. The order of pages is according to the phases of the protocol (induction, consolidation, re-induction and maintenance).

Outcome measurements

Event free survival (EFS) at 3 years was assessed. The EFS was measured from the date of at the time from diagnosis until the first date of treatment failure of any kind: treatment abandonment, death-toxicity or relapse-progressive disease. For patients still alive, event-free survival was calculated at the latest follow-up (censored observation).

Data analyses

Descriptive statistic was used to evaluate the demographic and medical characteristics of the patients. Differences in demographic and medical characteristic between the intervention and control group were assessed using chi-square test and Fischer exact test for nominal variables, and t-test for continuous variables. Kaplan Meier was used for the intent to treat analysis of the event-free-survival estimate. Cox regression analyses were used to assess the combined prognosis variables on survival. Other prognostic factors such as gender, risk-stratification, SES, protocol-used, transportation-time, parental education level were used as co-variants. All p values reported are two-sided. All analysis was conducted using the Statistical Package for Social Science (SPSS) version 12.

RESULTS

Patients' characteristics

During a period of January 2004 to February 2007, 124 patients were diagnosed with childhood ALL. Thirteen patients abandoned or died during the first-week, and 2 patients were hospitalized in PICU for 3-weeks and died. Fifty-six patients were assigned to the intervention group and fifty-three patients to control

group. Slightly more males (53%) were included. Most patients had poor SES background (83%). There were no significant differences between the intervention and the control groups regarding age, gender, transportation-time needed to the hospital, SES, parental educational background, used-protocol, risk-stratification, and receiving PEP. Ninety-four (86%) parents received a verbal explanation and an information-leaflet, 76 (70%) received a DVD, and 88 (81%) received an audiocassette (Table1). Fifteen (14%) parents did not receive any material of this PEP; all of them died or dropped-out in the first 3-weeks of treatment. The reasons for not receiving PEP were: the socio-pediatrician was not available, patients were too ill, and patients abandoned or died before PEP was given. At the time of analysis (September 2008), 24 (22%) patients abandoned treatment, 35 (32%) died, 13 (12%) relapsed, and 37 (43%) were alive and well. Seventeen of 35 (48%) had toxic-death during the induction phase.

Table 1. Demographic and medical characteristics

	Diary (n=56) n(%)	**Control (n=53) n(%)**	***p***
Age: mean±SD (years)	5.5±3.7	6.1±3.9	0.51
Gender			
Male (n=58)	25 (45)	33 (62)	0.07
Female (n=51)	31 (55)	20 (38)	
Fathers' education level			
Low (n=64)	36 (64)	28 (53)	0.26
High (n=45)	20 (36)	25 (47)	
Mothers' education level			
Low (n=59)	31 (55)	28 (52)	0.79
High (n=50)	25 (44)	25 (47)	
SES			
Poor (n=90)	44 (78)	46 (86)	0.53
Prosperous (n=19)	12 (22)	7 (14)	
Transportation-time			
1 hour (n=20)	11 (20)	9 (17)	0.92
2-3 hours (n=27)	14 (25)	13 (25)	
>3 hours (n=62)	31 (55)	31 (58)	
Risk			
SR (n=53)	29 (52)	26 (47)	0.77
HR (n=54)	27 (48)	27 (50)	
Protocol			
WK ALL (n=65)	33 (59)	32 (61)	0.89
Indonesian (n=44)	23 (41)	21 (39)	
Received PEP			
Verbal explanation (n=94)	47 (84)	47 (89)	0.56
Information booklet (n=94)	47 (84)	47(89)	0.56
Cassette (n=88)	44 (79)	40 (83)	0.39
DVD (n=76)	37 (66)	39 (83)	0.47

Overall EFS estimate at 3 years was 31%. The EFS estimate at 3 years in the intervention group and the control group were 42% vs. 21%, however it was no statistically significant difference (table 2).

Table 2. Event-Free Survival estimate at 3 years of childhood acute lymphoblastic leukemia, stratified by mothers' education level

	EFS estimate (%)	SE (%)	p
Overal			
Diary (n=56)	42	6	0.16
Control (n=53)	21	7	
Low mothers' education level			
Diary (n=31)	26	7	0.86
Control (n=28)	18	8	
High mother's education level			
Diary (n=25)	62	10	0.04
Control (n=25)	29	11	

Education level of mothers was the only significant predictor of treatment outcome, Odds ratio for treatment failure was 2.12 (95% CI 1.1-4.3) for low vs. high educational level of mothers. After being stratified by education level of mothers, among childhood ALL patients whose mothers had a high educational level, the EFS estimate at 3 years of the intervention group was significantly higher than the EFS estimate of the control group (62% vs. 29%, p=0.04) (figure1). No significant difference was found among patients whose mothers had a low educational level (26% vs. 18%, p=0.86) (figure 2). After combining mothers' educational level with randomization group, there was a significant result on treatment outcome. Compared to other groups, patients whose mothers had a high educational level and received a medication-diary book had the lowest treatment failure. Referring to this group (mothers with a high educational level and received a medication-diary book), the odds ratios for treatment failure were 2.6 (95% CI 1.1-5.9) for high mother's education-control group; 3.2 (95% CI 1.3-7.8) for low mothers' education-intervention group and 3.6 (95% CI 1.4-9.4) for low mothers' education-control group.

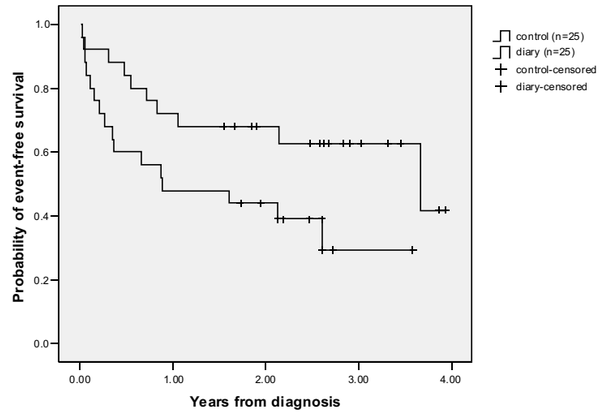

Figure1. Kaplan-Meier estimates of event-free survival of childhood acute lymphoblastic leukemia whose mothers' having high education level. Event included refusal or abandonment, toxic-death, and progressive or relapsed leukemia (p=0.04)

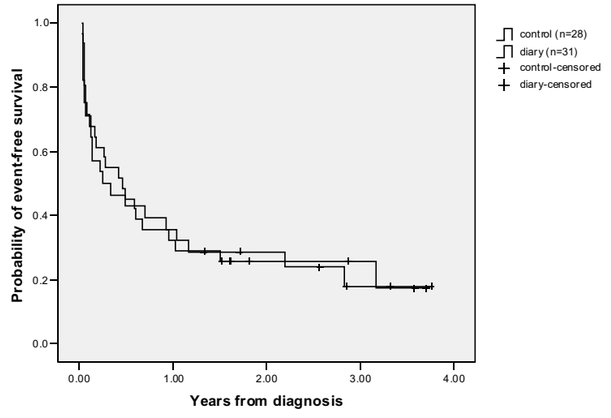

Figure 2. Kaplan-Meier estimates of event-free survival of childhood acute lymphoblastic leukemia whose mothers' having low education level. Event included refusal or abandonment, toxic-death, and progressive or relapsed leukemia (p=0.87)

DISCUSSION

This randomized study assessed the effectiveness of using a medication diary-book on the treatment outcome of childhood ALL in a pediatric-oncology center in a limited-resource setting. The aims of providing medication-diary books were to remind parents or patients to daily take their medications and remind them when the hospital should be visited. The parents were also encouraged to voluntarily write any information such as reasons for not taking the medications, symptoms, and others importance issues. The medication-diary books can also facilitate communication between parents/patients and health care providers. In order to achieve these benefits, a medication-diary book must be filled in. It needs motivation of parents or patients, and most importantly parents or patients should have an appropriate education background to be able to fill it in.

Our study found that in the overall sample population providing a medication-diary book clinically improved EFS estimates, even though statistically there was no significant difference. Providing a medication diary-book significantly improved the EFS estimates in childhood ALL patients whose mothers had a high educational level (senior high school or higher). We did not find any significant difference on EFS estimates among patients whose mothers had a low educational level. Even though we designed the medication-diary books to be simple and easy to fill in, for mothers with a low educational level it may still be difficult to fill in the diary. In addition, in our culture, where 12.1% of the population is analphabetic, using and writing in a diary is not common.

The effect of PEP might contribute the EFS estimate. In order to make easier to understand for all families even with a low educational background, we provide PEP with some approaches: verbal explanation, information-booklet, audiocassette, and DVD. This program was presented one time only, at the beginning of treatment. Families with a high educational background may understand the messages of PEP, even if they were only presented once. However, families with a low educational background may need more than one meeting to understand the messages of this program. A requisite for successful parental education programs is that patients must be active users: the information-booklet needs to be read, the audio-cassette must be listened to, and the DVD must be watched. We only assumed that all materials of PEP were used. Some studies found that repeated education -based on cognitive abilities of patients or parents- improved the knowledge and treatment outcome[11-12].

We also encouraged parents to bring the diary to the hospital during their visits, in order to be checked by an oncology-nurse. By checking the diary regularly, giving good comments and tailoring instruction of how to use of the diary-book, parents are stimulated to use the diary. Some studies found that positive reinforcement to perform desired behaviours is an effective behavioral strategy to improve self-management[13;14]. It is known that people have a greater tendency to use or do something, when they are often reminded to do. Unfortunately, the checking was seldom done. Two health care providers had the responsibility of signing the diaries. Assuming that both persons thought the other would fill in the diary, neither one do. Clear instructions need to be given to health care providers caring for diary users. One person should be responsible for the checks, and another person should be designated in case of absence of the responsible person. Another reason was both health providers had many duties besides checking the diary. Probably a check list at the policlinic can be helpful. It should contain items that should be asked at every visit such as: *Can I see your diary? Did you have difficulty in filling the diary? How many mercaptopurine pills does your child take each day? When do you give it? How many doses were missed in the past week? Did you have any fever?*

Our study was conducted in one hospital and this intervention could not be blinded both for health care providers and parents. We cannot prevent contamination effect of providing medication-diary books. Some mothers of childhood ALL patients in the control group created their own medication-diary book, because they perceived this book to be useful. This contamination may have diminished the difference outcome between the diary-group and the control-group.

We have analyzed some possible identified confounding factors such as risk-stratification, SES, gender, transportation-time to hospital, used-protocol. The analyses did not show that these factors contributed to the EFS estimate. However, since the treatment of ALL is long, complex and has side-effects, some other possible factors may have influenced the EFS estimate. We found that 24 (22%) patients abandoned treatment. Our exploratory study, in which families of children who abandoned treatment were interviewed, found that patients' experiences of severe side-effects and belief of ALL in-curability due to seeing other ALL patients die after receiving chemotherapy were main reasons for abandonment. We did not assess the parents' belief about curability as well as the occurrence of side effects.

Toxic-death was the most common cause of treatment failure, in which 35

(32%) patients had toxic-death. Infections are the most common causes of toxic-death in poor-resource settings, where supportive treatment is limited and most patients are malnourished[15-19]. Poor nutritional status decreases tolerance of chemotherapy, is associated with altered metabolism of chemotherapy and increased infection rate, resulting in poor clinical outcome [22;21] We also did not assess malnutrition in this study.

The study was conducted in one hospital, however; most patients were hospitalized in the third class and visited a general policlinic where they were treated by monthly-rotating residents with various knowledge, attitudes and skills. Some residents had better knowledge, better communication skills, more empathic approaches, and better skills in treating patients than other residents. The follow-up of this study is not long enough. Patients who still survive may have treatment failure. Further study in which more confounding factors are controlled and with a longer follow-up- is needed.

CONCLUSION

In a resource-limited setting, a medication-diary book is useful to improve the EFS estimate in childhood ALL patients especially in those whose mothers had a high education level. For parents with a lower educational level the diaries should be made simpler, and more support and education is necessary to help them to use it.

ACKNOWLEDGEMENT

We would like to thank Ignatius Purwanto for his excellent data management.

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